AMENDMENTS TO THE SPECIFICATION:

Please amend the specification as follows:

Please insert the following new paragraph before the first paragraph on page 1 of the specification:

This application is a divisional application of Application No. 09/635,359, filed August 9, 2000, which is a divisional application of Application No. 09/231,818, filed January 15, 1999, now U.S. Patent No. 6,171,846, which is a divisional application of Application No. 08/403,852, filed May 10, 1995, now U.S. Patent No. 5,891,695, which is the National Stage of International Application No. PCT/FR93/PCT00923, filed September 25, 1993, all of which are incorporated herein by reference.

Please replace the paragraph beginning on page 14, line 10, with the following amended paragraph:

Another subject of the present invention relates to the polypeptides resulting from the expression of the nucleotide sequences defined above. More especially, the present invention relates to polypeptides comprising all or part of the polypeptides SnaA (SEQ ID ~~no. 2~~ NO:17), SnaB (SEQ ID ~~no. 3~~ NO:18), SnaC (SEQ ID ~~no. 7~~ NO:22), SnaD (SEQ ID ~~no. 8~~ NO:23), PapA (SEQ ID ~~no. 9~~ NO:24), PapM (SEQ ID ~~no. 10~~ NO:25), SamS (SEQ ID ~~no. 4~~ NO:19), SnbA (SEQ ID ~~no. 5~~ NO:20), SnbC (SEQ ID ~~nos. 11 and 12~~ NO:26 and SEQ ID NO:27), SnbD (SEQ ID ~~nos. 13 and 14~~ NO:28 and SEQ ID NO:29), SnbE (SEQ ID ~~no. 15 and 16~~ NO:30 and SEQ ID NO:31) and SnbR (SEQ ID ~~no. 6~~ NO:21) or of derivatives of these. Within the meaning used in the present invention, the term derivative denotes any molecule obtained by modification of a genetic and/or chemical nature of the peptide sequence. Modification of a genetic and/or chemical nature is understood to mean any mutation, substitution, deletion, addition and/or modification of one or more residues. Such derivatives may be generated for different purposes, such as, in particular, that of increasing the affinity of the peptide for its substrate(s), that of improving its levels of production, that of increasing its resistance to proteases, that of increasing and/or modifying its activity, or that of endowing it with novel biological properties. Among derivatives resulting from an addition, there may be mentioned, for example, chimeric polypeptides containing an additional heterologous portion attached to one end. The term derivative also comprises polypeptides homologous to the polypeptides described in the present invention and originating from other cell sources, and in particular from strains producing streptogramins.

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Please replace the paragraph on page 37, lines 11-23, with the following amended paragraph:

The NH_2-terminal sequences of the proteins SnaA and SnaB, corresponding to the subunits of pristinamycin IIA synthase, were deduced by microsequencing. This is carried out by the Edman degradation technique, using an automated sequencer (Applied Biosystems model 407A) coupled to an HPLC apparatus for identification of the phenylthiohydantoin derivatives. About thirty residues were determined for each of them.
Protein SnaA: (see residues 2 to 29 on SEQ ID ~~No. 2~~ NO:17)
T A P(R) (R,W) R I T L A G I I D G P G G H V A A (W) R H P (A) T
Protein SnaB: (see residues 2 to 31 on SEQ ID ~~No. 3~~ NO:18)
T A P I L V A T L D T R G P A A T L G T I T (R) A V (R) A A E A

Please replace the paragraph beginning on page 37, line 24, and ending on page 38, line 4, with the following amended paragraph:

Moreover, sequences internal to these two polypeptides were determined after trypsin digestion of SnaA and SnaB and purification of the fragments obtained on a Vydac C18 HPLC column. The following internal sequences were found:
Protein SnaA: (see residues 365 to 384 on SEQ ID ~~No. 2~~ NO:17)
~~G A D G F N I D F P Y L P G S A D D F V~~
G A D G F N **I D F P Y L P G** S A D D F V
Protein SnaB: (see residues 122 to 136 on SEQ ID ~~No. 3~~ NO:18)
~~G L(-) D S F D D D A F V H D R~~
G L(-) D S **F D D D A F V H D** R

Please replace the paragraph on page 38, lines 5-14, with the following amended paragraph:

From the ~~underlined~~ bolded regions in each of the sequences of the fragments internal to the proteins SnaA and SnaB, and in accordance with the degeneracy of the genetic code specific to ~~Streptomyces~~ *Streptomyces* (see Example 8), the following mixtures of oligonucleotides were synthesized with a Biosearch 8600 automated synthesizer. They were then purified by the technique already described (Sawadogo M. and Von Dyke M. W., 1991). The ~~snaA~~ *snaA* and ~~snaB~~ *snaB* genes denote the structural genes for the proteins SnaA and SnaB, respectively.

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Please replace the paragraph on page 38, lines 15-20, with the following amended paragraph:

Mixture corresponding to the ~~underlined~~ bolded portion of the internal sequence of SnaA:

ATC GAC TTC CCC TAC CTC CCC GG
T T G T G G
A
T

(SEQ ID NO:32).

Please replace the paragraph on page 38, lines 21-25, with the following amended paragraph:

Mixture corresponding to ~~underlined~~ bolded portion of the internal sequence of SnaB :

TTC GAC GAT GAT GCA TTC GTC CAT GAC
C C T G C
C
G

(SEQ ID NO:33).

Please replace the paragraph on page 47, lines 7-10, with the following amended paragraph:

NH_2-terminal sequence of the protein 3-hydroxypicolinic:AMP ligase:
(See residues 1 to 21 on SEQ ID ~~No. 5~~ NO:20)
~~M L D G S V P W P E D V A A K Y R A A G Y~~
M L D G S **V P W P E D V A A K Y** R A A G Y

Please replace the paragraph on page 47, lines 11-14, with the following amended paragraph:

Internal sequence of the protein 3-hydroxypicolinic:AMP ligase:
(See residues 448 to 467 on SEQ ID ~~No. 5~~ NO:20)
~~V S A (-) E V E G H L G A H P D V Q Q A A~~
V S A (-) **E V E G H L G A H P D V Q Q** A A

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Please replace the paragraph on page 47, lines 15-19, with the following amended paragraph:

From the ~~underlined~~ bolded regions in each of the sequences, and in accordance with the degeneracy of the genetic code specific to ~~Streptomyces~~ *Streptomyces* (see Example 8), the following mixtures of oligonucleotides were synthesized:

Please replace the paragraph on page 47, lines 20-25, with the following amended paragraph:

Mixture corresponding to the ~~underlined~~ bolded portion of the NH_2-terminal sequence of the protein 3-hydroxypicolinic:AMP ligase:

5' 3'

GTC CCC TGG CCC GAG GAC GTC GCC GCC AGG TAC
G G G G G G

(SEQ ID NO:34).

Please replace the paragraph on page 48, lines 1-6, with the following amended paragraph:

Mixture corresponding to the ~~underlined~~ bolded portion of the internal sequence of the protein 3-hydroxypicolinic:AMP ligase:

5' 3'

GAG GTC GAG GGC CAC CTC GGC GCC CAC CCC GAC GTC CAG CAG GC
G G G G G G G

(SEQ ID NO:35).

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Please replace the paragraph on page 55, lines 14-20, with the following amended paragraph:

Sequences Internal to the Protein Pristinamycin I Synthase II
(See residues 49-61 on SEQ ID ~~No. 12~~ NO:27)

1 5 10
~~L A A F N D T A R P V P R~~
L A A F N D T A R P V P R

1 5 10 15 20
~~V P A A F V P L D A L P L T G N G V L D~~
V P A A **F V P L D A L P L** T G N G V L D
(SEQ ID NO:36).

Please replace the paragraph on page 55, lines 21-25, with the following amended paragraph:

From the ~~underlined~~ bolded regions in these sequences, and in accordance with the degeneracy of the genetic code specific to ~~Streptomyces~~ *Streptomyces* (see Example 8), the following mixtures of oligonucleotides were ~~snythesized~~ synthesized:

Please replace the paragraph on page 56, lines 1-6, with the following amended paragraph:

Mixture corresponding to the ~~underlined~~ bolded portion of the sequence 1 internal to the protein pristinamycin I synthase II:

5' 3'
GCC GCC TTC AAC GAC ACC GCC CGC CC
G G G G G
(SEQ ID NO:37).

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Please replace the paragraph on page 56, lines 7-12, with the following amended paragraph:

Mixture corresponding to the ~~underlined~~ bolded portion of sequence 2 internal to the protein pristinamycin I synthase II:

5' 3'
TTC GTC CCC CTC GAC GCC CTC CCC CT
G G G G G G
(SEQ ID NO:38).

Please replace the paragraph on page 63, lines 10-14, with the following amended paragraph:

Sequence internal to the protein pristinamycin I synthase III
~~1~~ (see residues 2 to 20 on SEQ ID ~~No. 13~~ NO:28)
1 5 10 15 20
~~P-VTPYRAYALAHLAG-DDD~~
P-**VTPYRAYAL**AHLAG-DDD

Please replace the paragraph on page 63, lines 15-18, with the following amended paragraph:

From the ~~underlined~~ bolded region in this sequence, and in accordance with the degeneracy of the genetic code specific to ~~Streptomyces~~ *Streptomyces* (see Example 8), the following mixture of oligonucleotides was synthesized:

Please replace the paragraph on page 63, lines 19-24, with the following amended paragraph:

Mixture corresponding to the ~~underlined~~ bolded portion of the sequence internal to the protein pristinamycin I synthase III:

5' 3'
GTC ACC CCG TAC CGC GCC TAC
G G C G G
(SEQ ID NO:39).

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Please replace the paragraph on page 72, lines 3-7, with the following amended paragraph:

Sequence internal to the protein pristinamycin I synthase IV
(See residues 82 to 98 on SEQ ID ~~No. 16~~ NO:31)

1 5 10 15

~~V T V F L N N T R L I Q N F R P P R - F - G D~~

V T V F L N N **T R L I Q N F R** P R - F - G D

Please replace the paragraph on page 72, lines 8-11, with the following amended paragraph:

From the ~~underlined~~ bolded region in this sequence, and in accordance with the degeneracy of the genetic code specific to ~~Streptomyces~~ *Streptomyces* (see Example 8), the following mixture of oligonucleotides was synthesized:

Please replace the paragraph on page 72, lines 12-18, with the following amended paragraph:

Mixture corresponding to the ~~underlined~~ bolded portion of the internal sequence of the protein pristinamycin I synthase IV:

5' 3'

ACG CGC CTC ATC CAG AAC TTC CGC CC
C G G G
T T

(SEQ ID NO:40).

Please replace the paragraph on page 79, lines 11-15, with the following amended paragraph:

NH_2-Terminal sequence of the protein FMN reductase
(See residues 2 to 25 on SEQ ID ~~No. 7~~ NO:22)

1 5 10 15 20 25

~~T G A D D P A R P A V G P Q S F R D A M A Q L A S P V~~

T G A D D P A R P A V G P Q S **F R D A M A Q L A** S P V

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Please replace the paragraph on page 79, lines 16-23, with the following amended paragraph:

Internal sequences of the protein FMN reductase:
(See residues 102 to 122 on SEQ ID ~~No. 7~~ NO:22)
1 5 10 15 20
~~F A G G E F A A W D G T G V P Y L P D A K~~
F A G G E F A A W D G T G V P Y L P D A K
(See residues 149 to 161 on SEQ ID ~~No. 7~~ NO:22)
1 5 10
~~T G D P A K P P L L W Y R~~
T G **D P A K P P L L W Y R**

Please replace the paragraph on page 79, lines 24-28, with the following amended paragraph:

From the ~~underlined~~ bolded regions in each of the sequences, and in accordance with the degeneracy of the genetic code specific to ~~Streptomyces~~ *Streptomyces* (see Example 8), the following mixtures of oligonucleotides were synthesized:

Please replace the paragraph on page 80, lines 1-5, with the following amended paragraph:

Mixture corresponding to the NH_2-terminal sequence of the protein FMN reductase:
5' 3'
TTC CGC GAC GCC ATG GCC CAG CTC GC
G G G G
(SEQ ID NO:41).

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Please replace the paragraph on page 80, lines 6-10, with the following amended paragraph:

Mixtures corresponding to the internal sequences of the protein FMN reductase:

5' 3'
TTC GCC GGC GGC GAG TTC GCC GCC TGG GAC GGC ACC GG
G G G G G G
(SEQ ID NO:42).

5' 3'
GAC CCC GCC AAG CCC CCC CTG CTG TGG TAC CG
G G G G C C
(SEQ ID NO:43).

Please replace the paragraph on page 91, lines 4-9, with the following amended paragraph:

In both cases the same residues are found, and this sequence corresponds exactly to the beginning of the protein sequence which is deduced from the sequence of the ~~papM~~ *papM* gene (see residues 2 to 11 on SEQ ID ~~No. 10~~ NO:25). The purified p-aminophenylalanine (phenyl-N)-methyltranferase is hence the protein PapM.

Please replace the paragraph on page 108, line 22 through page 109, line 10, with the following amended paragraph:

Frames 1 and 3 correspond respectively to the proteins SnaA (SEQ ID ~~no. 2~~ NO:17) and SnaB (SEQ ID ~~no. 3~~ NO:18) isolated above as described in Example 5 and for which the cloning of the genes is detailed in Example 6. In effect, the NH_2-terminal sequences of the products of ORFs 1 and 3 are identical to the NH_2-terminal sequences found for the proteins SnaA and SnaB, respectively, in Example 5.1.2, apart from the amino-terminal methionine which has been excized. Moreover, the molecular masses calculated from the sequences are comparable to the apparent molecular masses of the proteins SnaA and SnaB, estimated, respectively, in SDS-PAGE as described in Example 5.

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Please replace the paragraph on page 109, lines 20-24, with the following amended paragraph:

These sequence comparisons hence enable it to be demonstrated that the product of open reading frame no. 4 is an SAM synthase involved in the biosynthesis of pristinamycins I or II. This gene was designated ~~SamS~~ *samS* (SEQ ID ~~no.~~ NO: 4).

Please replace the paragraph on page 109, lines 25-28, with the following amended paragraph:

The demonstration of the involvement of the ~~SamS~~ *samS* gene in the biosynthesis of pristinamycins is confirmed by the construction of the SP92 mutant disrupted in this gene, as described in Example 9.2.

Please replace the paragraph on page 112, lines 8-13, with the following amended paragraph:

These data indicate that the product of the open reading frame contained in the 3.1-kb ~~BamHI-EcoRI~~ *Bam*HI-*Eco*RI fragment is a transport protein enabling pristinamycins I (and possible pristinamycins II) to be exported out of the cell. This protein was designated SnbR (SEQ ID NO:21) and the corresponding gene ~~snbR~~ *snbR* (SEQ ID ~~no.~~ NO:6).

Please replace the paragraph on page 112, line 23, through page 113, line 13, with the following amended paragraph:

The search for open reading frames for the 1050-bp fragment was performed as above. A single complete open reading frame could be demonstrated in this way. Its characteristics are as follows: this phase extends from position 84 to position 962 of the sequenced portion, which corresponds to a frame of 878 bases coding for a protein of 292 amino acids having a molecular mass of 32000 Da. This protein was referred to as protein PapM. It was, moreover, purified from ~~S. pristinaespiralis~~ *S. pristinaespiralis* strain SP92 as described in Example 5. The molecular mass of 32000 Da calculated

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from the sequence is identical to the apparent molecular mass of 32000 Da estimated on SDS-PAGE as described in Example 5. Moreover, the NH_2-terminal sequence of this protein, deduced as described in Example 5, corresponds well to the NH_2-terminal sequence of the protein PapM (SEQ ID NO:25) identified by analysis of the open reading frames of the sequence of 1050 bp (SEQ ID ~~no.~~ NO:10).

Please replace the paragraph on page 114, lines 12-16, with the following amended paragraph:

This confirms that cosmid pIBV3 isolated in Example 5.1 does indeed contain a portion of the structural gene for pristinamycin I synthase II described in Example 5.3, designated *snbC* ~~SnbC~~ (SEQ ID ~~no.~~ NO:11 and 12).

Please replace the paragraph on page 115, lines 19-23, with the following amended paragraph:

This confirms that cosmid pIBV3 isolated in Example 5.1 does indeed contain a portion of the structural gene for pristinamycin I synthase III described in Example 5.4, designated *snbD* ~~SnbD~~ (SEQ ID ~~nos.~~ NO:13 and 14).

Please replace the paragraph on page 116, lines 17-21, with the following amended paragraph:

This confirms that cosmid pIBV3 isolated in Example 5.1 does indeed contain a portion of the structural gene for pristinamycin I synthase IV described in Example 5.5, designated *snbE* ~~SnbE~~ (SEQ ID NO:15 and 16).

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Please replace the paragraph on page 116, line 27, through page 117, line 14, with the following amended paragraph:

The search for open reading frames for the 645-bp fragment was performed as above. An incomplete open reading frame could be demonstrated in this way. Its characteristics are as follows: this frame affords two possibilities for initiation of translation, a GTG at position 61 and a GTG at position 70 of the sequenced portion (the ATG located at position 124 was not taken into account owing to the sequence homologies described later). Analysis of the probabilities of the presence of Shine-Dalgarno regions does not make it possible to distinguish which of these codons corresponds to the initiation. No stop codon was identified, which indicates that this open reading frame is not terminated. The gene identified in this way was referred to as ~~papA~~ *papA* (SEQ ID NO:9), and the corresponding protein was referred to as protein PapA (SEQ ID ~~no. 9~~ NO:24).

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